REMARKS/ARGUMENTS

Status

Claims 155-159 and 161-179 were pending. New claim 180 is added by this amendment.

In the most recent Office Action, claims 155, 156, 158, 159, 161-167 and 169-171 were allowed. Claims 157 and 172-179 stand rejected. Applicants thank the Examiner for the rejoinder of claims 172-178, method claims depending from allowed claim 155. Claim 168, which also depends from claim 155 and therefore incorporates all of the limitations of an allowed claim, was not rejoined.

Applicants' responses to the rejections articulated by the Office are provided below. The Examiner is urged to contact the undersigned Applicants' representative should he feel an interview would facilitate examination.

Claim 173

Claim 173 was rejected under 35 USC 112, second paragraph as allegedly indefinite. Applicants have amended the claim as suggested by the Examiner. Applicants thank the Examiner for pointing out this typographical error.

Claim 157

Claim 157 was rejected under 35 USC 112, first paragraph, because the Office asserts human antibodies are not described in paragraph 149 of the specification. For the convenience of the Office, paragraph [0149] is reproduced below.

> [0149] The method described by Mendez et al. (1997) Nature Genetics 18:410 can be used. Briefly, purified antigen, is used to immunize transgenic mice lacking the native murine antibody repertoire and instead having most of the human antibody V-genes in the germ line configuration. **Human antibodies** are subsequently produced by the murine B cells. The antibody genes are recovered from the B cells by PCR library selection or classic hybridoma technology. (Emphasis added)

Applicants respectfully submit that "human antibodies" is clearly described, as indicated by the bolded portion of the excerpt above. The Office has asserted, incorrectly, "Regarding the transgenic mice of paragraph 149, said mice comprise only human V-genes, i.e., they do not comprise whole human monoclonal antibodies encompassed by the claims." A copy of the Mendez reference cited in paragraph [0149] was submitted in an IDS with the amendment filed August 19, 2004. The Mendez abstract reads:

> We constructed two megabase-sized YACs containing large contiguous fragments of the human heavy and kappa (kappa) light chain immunoglobulin (Ig) loci in nearly germline configuration, including approximately 66 VH and 32 V kappa genes. We introduced these YACs into Ig-inactivated mice and observed **human antibody production** which closely resembled that seen in humans in all respects, including gene rearrangement, assembly, and repertoire. Diverse Ig gene usage together with somatic hypermutation enables the mice to generate **high affinity fully human antibodies** to multiple antigens, including human proteins. Our results underscore the importance of the large Ig fragments with multiple V genes for restoration of a normal humoral immune response. These mice are likely to be a valuable tool for the generation of therapeutic antibodies. (emphasis added)

The comment by the Office that the reference describes only mice that "comprise only human V-genes" is not understood. Mendez is replete with description of production of transgenic mice comprising human immunoglobulin loci and capable of making fully human antibodies. See, for example, page 147, first column, first full paragraph.[1]

[1] Applicants also note the citation in paragraph [0150] of Maiti et al. (1997) Biotechnol. Int. 1:85-93 describing "**human hybridomas**."

Applicants respectfully submit human antibodies are described in the specification, and respectfully request this rejection be withdrawn. Should the Office continue to maintain human antibodies are not described the Examiner is respectfully urged to contact the undersigned Applicant's representative.

Rejections Under 35 USC 112, first paragraph (new matter)

Claims 172, 173, 174, 175, 176, 177, 178, and 179 as containing new matter. Applicants respectfully traverse for the reasons provided below.

Claim 172

Claim 172 reads: A method for preparing a population of cells enriched for BDCA-2^+ cells, comprising contacting a mixture of human cells with an antigen-binding fragment of claim 155 and isolating cells to which the antigen-binding fragment binds.

The Office states that paragraph 70 is a figure legend and not a generic method of preparing a population of cells. Paragraph 70 is a figure legend describing enriching a BDCA-2+ cells by contacting a mixture of human PBMCs with an anti-BDCA-2 antibody and isolating the cells to which the antibody binds. Applicants respectfully submit that paragraph 70 and the associated figure clearly demonstrate that Applicants "were in possession of the invention." Applicants respectfully submit that fact that paragraph 70 is a figure legend is of no consequence in determining compliance with Section 112. Further, support for this claim is replete in the specification. Paragraph 70 was cited as a demonstration of an actual reduction to practice of the subject matter. See, for example, paragraph [0087] ("The invention relates to methods of enriching for hematopoietic cell populations enriched in DCs and subsets thereof.")

Applicants have added new dependent claim 180. Support for this claim is found in the specification including, for example, at paragraph [0033] and original claim 62.

Claim 173

Claim 173 reads: A method of detecting BDCA-2 protein in a biological sample comprising (a) contacting the BDCA-2 protein with the antigen-binding fragment of claim 155

under conditions that permit formation of a complex between the BDCA-2 protein and the antigen-binding fragment; and (b) detecting the formation of the complex.

The Office states the paragraphs cited by the Applicants disclose only (1) a method of detecting BDCA-2-expressing DCs or (2) a method employing excess antigen-binding fragment. Applicants respectfully submit the disclosure is not limited to detecting DCs. For example, paragraph [0168] describes "methods of detecting . . . DCs and subsets thereof, in a biological sample and measuring antigens such as soluble BDCA-2, BDCA-3 or BDCA-4 and/or DCs in body fluids. The methods include obtaining a biological sample, contacting the sample with an antigen-binding fragment described herein under conditions that allow antibody-antigen-binding and detecting binding, if any, of the antibody to the sample as compared to a control, biological sample." Thus the specification describes detecting DCs *or* antigens, such as soluble antigens, is and does not require an excess of antigen-binding fragment. Reference to excess antigen-binding fragment is found in paragraph [0169] relates to a particular embodiment: the *description* is not limited to the particular embodiment. Further, Applications respectfully submit that the specification is replete with additional description of detecting BDCA-2+ protein. See, for example, paragraph [0108] "The use of . . . BDCA-2 . . . mAb provides a convenient and efficient way to rapidly detect, enumerate and isolate DC populations from PBMC, leukapheresis material, whole blood, tonsil, etc., without apparent functional perturbation." See, for example, Example 5, showing detection of BDCA-2+ cells. clearly demonstrate that Applicants "were in possession of the invention." Moreover, Applicants submit that immunoassays of all types are well know and that one of ordinary skill in the art would *immediately recognize* from the detailed description of anti-BDCA-2 antibodies and description (and common knowledge of) immunoassays that the inventors were clearly in possession of methods for detecting antigen as claimed! Section 112 does not require more than this.

Claim 174

Claim 174 reads "The method of claim 173 wherein the BDCA-2 protein is displayed on the surface of a dendritic cell." That is, the antigen detected according to the method of claim 173 is cell-bound BDCA-2+. Applicants are confused by this rejection in view of the comment

by the Office that in connection with claim 173 that "the cites [i.e., paragraphs] disclose a method of detecting BDCA-2-expressing DCs." The specification is replete, of course, with teaching that BDCA-2+ is found on the surface. See for example, paragraph [0103] describing BDCA-2 as a surface marker. Paragraph 110 was cited because it describes "detecting, enumerating and/or isolating DCs . . ." That is, it describes use of anti-BDCA-2+ antigen binding fragments to detect *dendritic cells* expressing the antigen.

Claims 175 and 176

Claim 175 reads: The method of claim 174 wherein the step of detecting the formation of the complex comprises detecting at least one metabolic change in the dendritic cell.

Claim 176 reads: The method of claim 175 wherein the metabolic change is down-regulation of type I interferon production, down-regulation of Th1 immune responses, induction of intracellular Ca^{2+} mobilization, or polarization of an immune response to Th2.

The Office acknowledges that claims 175 and 176 are described with regard to monoclonal antibody AC144 but asserts that the description does not extend to other antibodies..

Paragraph [0240] discloses "The invention further includes down-regulation of type I interferon production via ligation of BDCA-2, down-regulation of Thl immune responses via ligation of BDCA-2, and polarization of an immune response to Th2 via ligation of BDCA." Nowhere does the specification suggest this ligation is limited to a single specific monoclonal antibody and no person of skill reading the specification would conclude that the AC144 antibody is *unique* in having this property. The Office appears to assert that because AC144 is *exemplified* no other antibody is described. Applicants respectfully submit this is not a correct application of the written description requirement of Section 112, and respectfully submit this rejection should be withdrawn.

Claim 177

Claim 177 reads "A method of ligating BDCA-2 antigen on a dendritic cell comprising contacting the cell with the antigen-binding fragment of claim 155." Paragraph [0240] discloses "The invention further includes down-regulation of type I interferon production via ligation of

BDCA-2, down-regulation of Thl immune responses via ligation of BDCA-2, and polarization of an immune response to Th2 via ligation of BDCA." Nowhere does the specification suggest this ligation is limited to a single specific monoclonal antibody and no person of skill reading the specification would conclude that the AC144 antibody is *unique* in having this property. The Office appears to assert that because AC144 is *exemplified* no other antibody is described. Applicants respectfully submit this is not a correct application of the written description requirement of Section 112, and respectfully submit this rejection should be withdrawn. The Office is respectfully reminded that the Courts have recognized that monoclonal antibody technology is a well known technology. See, e.g., *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) ["For example, the PTO would find compliance with § 112, ¶ 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature."] .

Claim 178

To expedite prosecution Claim 178 has been amended without out prejudice to future prosecution of the unamended claim. Support for the amendments is replete in the application as filed including, for example, paragraph [0041] and original claim 93.

Claim 179

The Office states that paragraph 208 "discloses a reagent capable of binding with the first reagent . . . only *after it has found its target*, which would imply a conformational dependence." The Office has improperly introduced the word "only" and thereby distorted the meaning of the paragraph (reproduced below for the convenience of the Office). In fact, this paragraph describes a conventional assay in which an unlabeled antibody is bound to its antigen and then labeled with a second reagent such as an labeled anti-immunoglobulin antibody (e.g., labeled anti-murine IgG is used to label a murine anti-BDCA2 antibody). Likewise, labeled avidin can be used to label a biotin labeled anti-BDCA-2 antibody. The reason the paragraph

describes labeling "after" the first antibody has bound is because, as is conventional in the art, this is what allows the practitioner *to detect the target.*

> [0208] Optionally, the reagent can be conjugated with a label to permit detection of any complex formed with the target in the sample. In another option, a second reagent is provided that is capable of combining with the first reagent after it has found its target and thereby supplying the detectable label. For example, labeled anti-murine IgG can be provided as a secondary reagent. Labeled avidin is a secondary reagent when the primary reagent has been conjugated to biotin.

Rejection of Claims 175 and 176 Under 35 USC 112, First Paragraph as Allegedly Not Enabled

Claims 175 and 176 were rejected under Section 112, the Office asserting that the specification did not enable the claimed method.

The Office asserts that specification only exemplifies use of one antibody, AC144. The Office states that "given the novelty of BDCA-2 antigen binding fragments, the specification must be looked to for guidance regarding the possible uses of said antigen binding fragments." The Office states that "for example, certain anti-CD3 antibodies are capable of activation T cells whereas others actually block T cell activation."

The test for enablement is not whether every anti-BDCA-2 antibody would have the same activity as AC144, but rather whether other antibodies with this activity could be identified based on the specification without undue experimentation. Given the routine nature of antibody production and screening (see *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), and provided with the guidance of the specification, Applicants submit that absent evidence from the Office that the properties of AC144 are unique, it is clear that the enablement by the specification is not limited to the exemplified antibodies.

The Office also states that the antibody was used with a second cross-linking agent. The "second" agent (e.g., a secondary cross-linking antibody) merely served to link the cell-bound anti-BDCA-2 antibodies. There is nothing special about the secondary antibody (or

other cross-linker) -- for example, commercially available rat anti-mouse IgG1 is used in Example 13. The second agent is a commonly available, generic reagent and the specification is entirely enabling for the use of such reagents.

Applicants respectfully request this rejection be withdrawn for the reasons provided above.

Rejoinder

Applicants thank the Examiner for the rejoinder of claims 172-178, method claims depending from allowed claim 155. The Office stated that the claim was directed to a non-elected invention. Applicants respectfully disagree. Claim 168 depends from claim 155 and therefore incorporates all of the limitations of an allowed claim. Claims 168 is directed to an anti-BDCA-2 antigen-binding fragment of claim 155, the elected invention, which fragment is bound to a dendritic cell, to which an anti-BDCA-4 antibody is also bound. Further, Applicants submit that, given the Examiner has already carefully examined the application there is little if any burden to establishing that some dendritic cell express BDCA-4 and anti BDCA-4 antibodies are clearly described and enabled by the specification (which provides the sequence of the antigen and teaches in detail how to make antibodies). The Office would not be required to review the art, the novelty and nonobviousness of the claim having already been established. Accordingly, Applicants respectfully request the Examiner to reconsider and rejoin claim 168.

Sequence Listing

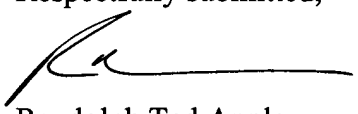
Applicants submit a second substitute sequence listing to correctly present SEQ ID NO:2 as a human sequence. The second substitute sequence listing, presented in computer readable format, was prepared through the use of the software program "PatentIn Version3.0" and is identical to that of the paper copy of the second substitute sequence listing in the Appendix. In addition, the specification has been amended to conform to the second substitute sequence listing. Support for the amendments to the sequence listing and specification may be found, *e.g.*, at page 23, lines 4-5, and in Figure 23 of the original application. These amendments contain no new matter.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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Attachments
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APPENDIX: Second Substitute Sequence Listing